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L8 and liposome	70

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US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L9

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Search History

DATE: Tuesday, January 09, 2007 **Purge Queries** Printable Copy Create Case

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L9	L8 and liposome	70	L9
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L7	L4 and liposome	1713	L7
L6	L4 and L1	0	L6
L5	L4 and l1	0	L5
L4	peripheral adj1 arter$	8142	L4
L3	L1 and 424/450.ccls.	13	L3
L2	L1 and acetyl$carnitine	4	L2
L1	liposome same $carnitine	430	L1

END OF SEARCH HISTORY

L2: Entry 3 of 4 File: PGPB Jan 30, 2003

DOCUMENT-IDENTIFIER: US 20030022859 A1
TITLE: Method for increasing the gene expression of transfected genes

Summary of Invention Paragraph:
[0005] Treatment with acetyl L-carnitine in cell clones transfected using known techniques, e.g. liposomes, considerably increases the expression of proteins coded for by the transfected genes.

Detail Description Paragraph:
[0012] Treatment with acetyl-L-carnitine (ALC). 4.times.10.sup.6 and 5.times.10.sup.6 cells cultured in a medium containing ALC at final concentrations of 5 mM and 10 mM, respectively, were seeded in two 125 cm.sup.3 flasks, whereas 2.times.10.sup.6 cells not treated with ALC were plated in a 75 cm.sup.3 flask. The treatment was repeated after 48 h (coinciding with the seeding of the cells for transfection) and after 72 h (at the end of transfection) and was also repeated after 120 h only in the case of samples transfected for lysis at 72 h.

Hit List

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Search Results - Record(s) 1 through 13 of 13 returned.

☐ 1. Document ID: US 20060222695 A1

L3: Entry 1 of 13 File: PGPB Oct 5, 2006

PGPUB-DOCUMENT-NUMBER: 20060222695
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060222695 A1

TITLE: Deoxycholic acid liposome-based dermatological topical preparation

PUBLICATION-DATE: October 5, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Zadini; Filiberto	North Hills	CA	US
Zadini; Giorgio	Camarillo	CA	US

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20060110439 A1

L3: Entry 2 of 13 File: PGPB May 25, 2006

PGPUB-DOCUMENT-NUMBER: 20060110439
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060110439 A1

TITLE: Dermal delivery of n-methyl-glucamine and n-methyl-glucamine compounds

PUBLICATION-DATE: May 25, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Tobia; Annette	Wyndmoor	PA	US
Kappler; Francis	Philadelphia	PA	US

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 3. Document ID: US 20050079209 A1

L3: Entry 3 of 13 File: PGPB Apr 14, 2005

PGPUB-DOCUMENT-NUMBER: 20050079209
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050079209 A1

TITLE: Esters of L-carnitine of alkanoyl L-carnitines useful as cationic lipids for the intracellular delivery of pharmacologically active compounds

PUBLICATION-DATE: April 14, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Pisano, Claudio	Aprilia (LT)		IT
Tinti, Maria Ornella	Rome		IT
Santaniello, Mose	Nettuno (RM)		IT
Critelli, Luciana	Pomezia (RM)		IT
Salvatori, Giovanni	Rome		IT

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 4. Document ID: US 20020039595 A1

L3: Entry 4 of 13 File: PGPB Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020039595
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020039595 A1

TITLE: ORAL LIPOSOMAL DELIVERY SYSTEM

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
KELLER, BRIAN C.	ANTIOCH	CA	US

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 5. Document ID: US 6897196 B1

L3: Entry 5 of 13 File: USPT May 24, 2005

US-PAT-NO: 6897196

DOCUMENT-IDENTIFIER: US 6897196 B1
** See image for Certificate of Correction **

TITLE: pH sensitive lipids based on ortho ester linkers, composition and method

DATE-ISSUED: May 24, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Szoka, Jr.; Francis C.	San Francisco	CA		
Guo; Xin	San Francisco	CA		

US-CL-CURRENT: 514/1; 424/450, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Drawing D

☐ 6. Document ID: US 6797281 B1

L3: Entry 6 of 13 File: USPT Sep 28, 2004

US-PAT-NO: 6797281
DOCUMENT-IDENTIFIER: US 6797281 B1
** See image for Certificate of Correction **

TITLE: Esters of I-carnitine or alkanoyl I-carnitines

DATE-ISSUED: September 28, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pisano; Claudio	Aprilia			IT
Tinti; Maria Ornella	Rome			IT
Santaniello; Mose	Nettuno			IT
Critelli; Luciana	Pomezia			IT
Salvatori; Giovanni	Rome			IT

US-CL-CURRENT: 424/450; 424/43, 424/434, 424/449, 424/46, 514/506, 554/30

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Drawing D

☐ 7. Document ID: US 6726924 B2

L3: Entry 7 of 13 File: USPT Apr 27, 2004

US-PAT-NO: 6726924
DOCUMENT-IDENTIFIER: US 6726924 B2

TITLE: Oral liposomal delivery system

DATE-ISSUED: April 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Keller; Brian C.	Antioch	CA		

US-CL-CURRENT: 424/450; 424/451, 424/452, 424/453, 424/455, 424/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 8. Document ID: US 6355270 B1

L3: Entry 8 of 13 File: USPT Mar 12, 2002

US-PAT-NO: 6355270
DOCUMENT-IDENTIFIER: US 6355270 B1
** See image for Certificate of Correction **

TITLE: Particles for oral delivery of peptides and proteins

DATE-ISSUED: March 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ferrari; Mauro	Dublin	OH		
Dehlinger; Peter J.	Palo Alto	CA		
Martin; Francis J.	San Francisco	CA		
Grove; Carl F.	Portola Valley	CA		
Friend; David R.	Menlo Park	CA		

US-CL-CURRENT: 424/489; 424/185.1, 424/450, 424/451, 514/2, 514/21, 530/300, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 9. Document ID: US 5876747 A

L3: Entry 9 of 13 File: USPT Mar 2, 1999

US-PAT-NO: 5876747
DOCUMENT-IDENTIFIER: US 5876747 A

TITLE: Liposome preferentially traveling to cardiac and skeletal muscles

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stracher; Alfred	Roslyn Estates	NY	11576	
Kesner; Leo	Brooklyn	NY	11234	

US-CL-CURRENT: 424/450; 514/78, 514/821, 554/79, 554/80

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 10. Document ID: US 5626869 A

L3: Entry 10 of 13 File: USPT May 6, 1997

US-PAT-NO: 5626869
DOCUMENT-IDENTIFIER: US 5626869 A
** See image for Certificate of Correction **

TITLE: Pharmaceutical composition containing a defined lipid system

DATE-ISSUED: May 6, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nyqvist; H.ang.kan	Tullinge			SE
Einarsson; Monica	Upsala			SE
Mattsson; Christer	Kungsbacka			SE

US-CL-CURRENT: 424/450; 264/4.1, 424/489, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 11. Document ID: US 5008288 A

L3: Entry 11 of 13 File: USPT Apr 16, 1991

US-PAT-NO: 5008288
DOCUMENT-IDENTIFIER: US 5008288 A

TITLE: Carnitine directed pharmaceutical agents

DATE-ISSUED: April 16, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stracher; Alfred	Roslyn Estates	NY	11576	
Kesner; Leo	Brooklyn	NY	11234	

US-CL-CURRENT: 514/535; 424/450, 428/402.2, 514/17, 514/2, 514/305, 514/547, 514/556, 514/821, 530/330, 530/812

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 12. Document ID: US 4866040 A

L3: Entry 12 of 13 File: USPT Sep 12, 1989

US-PAT-NO: 4866040
DOCUMENT-IDENTIFIER: US 4866040 A

TITLE: Aminocarnitine directed pharmaceutical agents

DATE-ISSUED: September 12, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stracher; Alfred	Roslyn Estates	NY	11576	
Kesner; Leo	Brooklyn	NY	11234	

US-CL-CURRENT: 514/17; 424/450, 428/402.2, 514/2, 514/305, 514/535, 514/547, 514/556, 514/78, 514/821, 530/330, 930/10, 930/250, 930/30

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 13. Document ID: EP 279887 A2

L3: Entry 13 of 13 File: EPAB Aug 31, 1988

PUB-NO: EP000279887A2
DOCUMENT-IDENTIFIER: EP 279887 A2
TITLE: Carnitine directed pharmaceutical agents and their use for the manufacture of a medicament for the treatment of muscle disorder.

PUBN-DATE: August 31, 1988

INVENTOR-INFORMATION:

NAME	COUNTRY
STRACHER, ALFRED	

US-CL-CURRENT: 424/450
INT-CL (IPC): A61K 9/50; A61K 37/64; A61K 47/00; C07C 101/30; C07C 103/50; C07C 149/247; C07K 5/02
EUR-CL (EPC): A61K009/127; A61K047/48, A61K047/48 , C07C229/22 , C07C229/26 , C07C323/58 , C07K005/02 , C07K005/06

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

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L3: Entry 13 of 13 File: EPAB Aug 31, 1988

DOCUMENT-IDENTIFIER: EP 279887 A2
TITLE: Carnitine directed pharmaceutical agents and their use for the manufacture of a medicament for the treatment of muscle disorder.

Abstract Text (1):
CHG DATE=19990617 STATUS=O> Carnitine, aminocarnitine and cysteic acid serve as carriers to bring pharmaceutically active compounds to desired sites in the body, e.g. skeletal muscle or to the heart. The pharmaceutically active compound can be a protease inhibitor, a cardioactive drug for combating arrythmia, etc. The linkage is chemical through one or more alcohol, carboxyl or amine groups using reagents such as glutaraldehyde, dicarboxylic acid anhydrides and acid halides and carbodiimdes. Carnitine derivatives are also incorporated into liposomes which are then used as carriers of active pharmaceutical agents.

Current US Cross Reference Classification (1):
424/450

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L3: Entry 12 of 13 File: USPT Sep 12, 1989

DOCUMENT-IDENTIFIER: US 4866040 A
TITLE: Aminocarnitine directed pharmaceutical agents

Abstract Text (1):
Carnitine, aminocarnitine and cysteic acid serve as carriers to bring pharmaceutically active compounds to desired sites in the body, e.g. skeletal muscle or the heart. The pharmaceutically active compound can be a protease inhibitor, a cardioactive drug for combating arrythmia, etc. The linkage is chemical through one or more alcohol, carboxyl or amine groups using reagents such as glutaraldehyde, dicarboxylic acid anhydrides and acid halides and carbodiimides. Carnitine derivatives are also incorporated into liposomes which are then used as carriers of active pharmaceutical agents.

Brief Summary Text (41):
In accordance with another aspect of the invention, the carrier which brings the active material to the predetermined site, e.g. carnitine for muscle, can be chemically linked to a phosphatide in the form of a liposome. The pharmaceutically active compound then exists enclosed as an aqueous solution inside the liposome. The chemical linkage between carrier and phosphatic can be direct or indirect, e.g. through a linking agent coupled to the phosphatide and to carnitine, aminocarnitine or cysteic acid.

Brief Summary Text (42):
Carnitine can be incorporated into liposomes in a number of ways and still retain the carbonyl and trimethylamine functional groups needed for the recognition of the carnitine receptor site. One way to do this is to use phosphatidylcarnitine or a mixture of phospholipids and lipids containing some fraction of its components as phosphatidylcarnitine. Phosphatidylcarnitine is synthesized from phosphatidic acid of desired fatty acid composition, optical activity and any other characteristics required. This is then reacted with the phthalimidomethyl ester of carnitine using triisopropylbenzenesulfonyl chloride in pyridine as the condensing agent. The ester protecting group is then removed using sodium thiophenoxide as hydrolyzing agent to yield phosphatidylcarnitine (XXXIV).

Brief Summary Text (43):
The procedure is similar to that described by Browning, J. and Seeling, J., Chem. Phys. Lipids 24, 103 (1979) for the synthesis of phosphatidylserine and phosphatidylcholine. Numerous other procedures utilizing other protecting goups and condensing agents have been reported (Chadha, J. S., Biochem. Piophys. Acta 248, 455 (1971), Rosenthal, A. F., Methods in Enzymology 358, 429 (1975), and Eibl, H. In Liposomes: From Physical Structure to Therapeutic Applications, ed. C. G. Knight, Elsevier/North-Holland Biomedical Press, N.Y., 1981 pp19-49. In the following reactions it may be necessary to protect the COO.sup.- group of the carnitine moiety with a suitable blocking group as per the more detailed procedure of example 4 (XXXV). ##STR21## wherein R.sub.1 and R.sub.2 are hydrocarbon chains of 6-20 carbon atoms, saturated or unsaturated.

Brief Summary Text (44):
Liposomes containing propranolol or any other pharmaceutical agents are made with mixtures of phosphatidyl carnitine and other phosholipids and lipids. Examples are

phosphatidylcarnitine, cholesterol (85:15) (molar ratios); phosphatidylcarnitine, phosphatidylcholine, cholesterol (20:70:10); phosphatidylcarnitine, cholesterol, stearylamine (50:10:40); phosphatidalcarnitine, phosphatidylserine, cholesterol (45:45:10).

Brief Summary Text (45):
Carnitine can also be added to liposomes by covalent linkage of carnitine to phospholipids with available functional groups. Then these derivatized phospholipids can be made into liposomes directly or mixed with other phospholipids and then made into liposomes.

Brief Summary Text (51):
In the past, a major drawback to the use of liposomes are vectors for drug delivery has been the fact that when injected into the blood stream they are taken up predominantly by the liver and reticuloendothelial system so that drugs active in disease conditions affecting other organs cannot be delivered efficiently by this procedure. In addition, liposomes cannot be administered orally because pancreatic lipase enzymes in the intestine break down the liposomes during digestion. The present invention offers a means of eliminating both of these drawbacks. Because of the presence of carnitine or aminocarnitine as part of the liposomal structure, the drug-containing liposomes will be delivered in much greater amounts to the desired target organs and much less will be metabolized by the liver. In addition, the presence of phosphatidyl carnitine in the liposome structure will present the intestinal lipase enzymes with a novel chemical structure that is apt to be far more resistant to digestion than naturally occurring lipids. This also holds true for liposomes containing amino carnitine and would serve to facilitate oral administration of organ specific pharmacologically active agents.

Brief Summary Text (52):
The specifications for such treatment vary with the type of clinical condition sought to be alleviated. For cases of severe arrhythmia, propranolol hydrochloride is usually administered intravenously (Goodman, L.S. and Gilman, A. G., The Pharmacological Basis of Therapeutics, 7th edition, Macmillan 1985, p. 197). Such a procedure is facilitated by using the drug in its site-directed, liposome-enveloped form. Thus, a suspension of phosphatidylcarnitine-linked liposomes loaded with a therapeutically effective dose (up to 3 mg) of propranolol hydrochloride in a total of 1 ml saline is injected intravenously into a patient suffering from severe arrhythmia. Blood pressure is then continually monitored with subsequent injections of propranolol-loaded liposomes as needed. This same procedure can be used effectively for other cardioactive drugs.

Brief Summary Text (53):
Propanolol has also been administered orally in doses of 40-320 mg per day to control arrhythmia and high blood pressure (Goodmand and Gilman, supra, p. 197). Although liposomes have heretofore been of little value in oral administration of drugs, the presence of phosphatidylcarnitine presents the inactivating intestinal lipases with a novel structure which will not be as readily degraded. Phosphatidylcarnitine-linked liposomes loaded with a physiologically effective dose of propranolol hydrochloride (or some other cardioactive substance) can be given orally in a slow-release capsule. After entering the bloodstream, the liposomes are directed, by the phosphatidylcarnitine structure, to be selectively taken up by the heart (to the exclusion of other organs).

Detailed Description Text (33):
Preparation of Liposome containing phosphatidylcarnitine

Detailed Description Text (35):
Liposomes are prepared by standard procedures. Thus 5 mg phosphatidylcarnitine is dissolved in 1 ml chloroform-methanol (2:1) in a small glass tube. To this solution is added 2 mg propranolol and the mixture of nitrogen gas and to the dry film is

added 1 ml phosphate buffer pH 7.4, 0.01 M. The tube is sonicated in 200 Watt bath type sonicator for 15 minutes at room temperature. The contents are then filtered through a 1.2 um membrane filter and the liposomes are separated from the unencapsulated propranolol by chromatography on a 0.9.times.20 cm Sepharose 6B column.

Current US Cross Reference Classification (1):
424/450

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L3: Entry 10 of 13 File: USPT May 6, 1997

DOCUMENT-IDENTIFIER: US 5626869 A
** See image for Certificate of Correction **
TITLE: Pharmaceutical composition containing a defined lipid system

Brief Summary Text (17):
Furthermore, derivatives of lipids may also be used in combination with the above mentioned lipids. One examples of this is polyethylene glycol coupled to phosphatidylethanolamine, which has shown to prolong the circulation time of liposomes after injection in the blood stream. Another example of such a derivative is palmitoylcarnitine, which acts as an absorption enhancer for bioactive substances in the gut.

Current US Original Classification (1):
424/450

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L3: Entry 9 of 13 File: USPT Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5876747 A
TITLE: Liposome preferentially traveling to cardiac and skeletal muscles

Abstract Text (1):
Carnitine, aminocarnitine and cysteic acid serve as carriers to bring pharmaceutically active compounds to desired sites in the body, e.g. skeletal muscle or the heart. The pharmaceutically active compound can be a protease inhibitor, a cardioactive drug for combating arrythmia, etc. The linkage is chemical through one or more alcohol, carboxyl or amine groups using reagents such as glutaraldehyde, dicarboxylic acid anhydrides and acid halides and carbodiimides. Carnitine derivatives are also incorporated into liposomes which are then used as carriers of active pharmaceutical agents.

Brief Summary Text (41):
In accordance with another aspect of the invention, the carrier which brings the active material to the predetermined site, e.g. carnitine for muscle, can be chemically linked to a phosphatide in the form of a liposome. The pharmaceutically active compound then exists enclosed as an aqueous solution inside the liposome. The chemical linkage between carrier and phosphatic can be direct or indirect, e.g. through a linking agent coupled to the phosphatide and to carnitine, aminocarnitine or cysteic acid.

Brief Summary Text (42):
Carnitine can be incorporated into liposomes in a number of ways and still retain the carbonyl and trimethylamine functional groups needed for the recognition of the carnitine receptor site. One way to do this is to use phosphatidylcarnitine or a mixture of phospholipids and lipids containing some fraction of its components as phosphatidylcarnitine. Phosphatidylcarnitine is synthesized from phosphatidic acid of desired fatty acid composition, optical activity and any other characteristics required. This is then reacted with the phthalimidomethyl ester of carnitine using triisopropylbenzenesulfonyl chloride in pyridine as the condensing agent. The ester protecting group is then removed using sodium thiophenoxide as hydrolyzing agent to yield phosphatidylcarnitine (XXXIV).

Brief Summary Text (43):
The procedure is similar to that described by Browning, J. and Seeling, J., Chem. Phys. Lipids 24, 103 (1979) for the synthesis of phosphatidylserine and phosphatidylcholine. Numerous other procedures utilizing other protecting groups and condensing agents have been reported (Chadha, J. S., Biochem. Piophys. Acta 248, 455 (1971), Rosenthal, A. F., Methods in Enzymology 358, 429 (1975), and Eibl, H. in Liposomes: From Physical Structure to Therapeutic Applications, ed. C. G. Knight, Elsevier/North-Holland Biomedical Press, New York, 1981 pp19-49. In the following reactions it may be necessary to protect the COO.sup.- group of the carnitine moiety with a suitable blocking group as per the more detailed procedure of example 4 (XXXV). ##STR21## wherein R.sub.1 and R.sub.2 are hydrocarbon chains of 6-20 carbon atoms, saturated or unsaturated.

Brief Summary Text (44):
Liposomes containing propranolol or any other pharmaceutical agents are made with mixtures of phosphatidyl carnitine and other phosholipids and lipids. Examples are

phosphatidylcarnitine, cholesterol (85:15) (molar ratios); phosphatidylcarnitine, phosphatidylcholine, cholesterol (20:70:10); phosphatidylcarnitine, cholesterol, stearylamine (50:10:40); phosphatidylcarnitine, phosphatidylserine, cholesterol (45:45:10).

Brief Summary Text (45):
Carnitine can also be added to liposomes by covalent linkage of carnitine to phospholipids with available functional groups. Then these derivatized phospholipids can be made into liposomes directly or mixed with other phospholipids and then made into liposomes.

Brief Summary Text (51):
In the past, a major drawback to the use of liposomes as vectors for drug delivery has been the fact that when injected into the blood stream they are taken up predominantly by the liver and reticuloendothelial system so that drugs active in disease conditions affecting other organs cannot be delivered efficiently by this procedure. In addition, liposomes cannot be administered orally because pancreatic lipase enzymes in the intestine break down the liposomes during digestion. The present invention offers a means of eliminating both of these drawbacks. Because of the presence of carnitine or aminocarnitine as part of the liposomal structure, the drug-containing liposomes will be delivered in much greater amounts to the desired target organs and much less will be metabolized by the liver. In addition, the presence of phosphatidyl carnitine in the liposome structure will present the intestinal lipase enzymes with a novel chemical structure that is apt to be far more resistant to digestion than naturally occurring lipids. This also holds true for liposomes containing amino carnitine and would serve to facilitate oral administration of organ specific pharmacologically active agents.

Brief Summary Text (52):
The specifications for such treatment vary with the type of clinical condition sought to be alleviated. For cases of severe arrhythmia, propranolol hydrochloride is usually administered intravenously (Goodman, L. S. and Gilman, A. G., The Pharmacological Basis of Therapeutics, 7th edition, Macmillan 1985, p. 197). Such a procedure is facilitated by using the drug in its site-directed, liposome-enveloped form. Thus, a suspension of phosphatidylcarnitine-linked liposomes loaded with a therapeutically effective dose (up to 3 mg) of propranalol hydrochloride in a total of 1 ml saline is injected intravenously into a patient suffering from severe arrhythmia. Blood pressure is then continually monitored with subsequent injections of propranolol-loaded liposomes as needed. This same procedure can be used effectively for other cardioactive drugs.

Brief Summary Text (53):
Propanolol has also been administered orally in doses of 40-320 mg per day to control arrhythmia and high blood pressure (Goodman and Gilman, supra, p. 197). Although liposomes have heretofore been of little value in oral administration of drugs, the presence of phosphatidylcarnitine presents the inactivating intestinal lipases with a novel structure which will not be as readily degraded. Phosphatidylcarnitine-linked liposomes loaded with a physiologically effective dose of propranolol hydrochloride (or some other cardioactive substance) can be given orally in a slow-release capsule. After entering the bloodstream, the liposomes are directed, by the phosphatidylcarnitine structure, to be selectively taken up by the heart (to the exclusion of other organs).

Detailed Description Text (34):
Preparation of Liposomes Containing Phosphatidylcarnitine Which Encapsulate Propranalol

Detailed Description Text (35):
Liposomes are prepared by standard procedures, Thus 5 mg phosphatidylcarnitine is dissolved in 1 ml chloroform-methanol (2:1) in a small glass tube. To this solution

is added 2 mg propranolol and the mixture is vortexed. The solvent is evaporated with a stream of nitrogen gas and to the dry film is added 1 ml phosphate buffer pH 7.4, 001 M. The tube is sonicated in 200 Watt bath type sonicator for 15 minutes at room temperature. The contents are then filtered through a 1.2 um membrane filter and the liposomes are separated from the unencapsulated propranolol by chromatography on a 0.9.times.20 cm Sepharose 6B column.

Current US Original Classification (1):
424/450

CLAIMS:

1. A liposome which preferentially travels to cardiac and skeletal muscles, comprising a phosphatide chemically linked to a member selected from the group consisting of carnitine, aminocarnitine and cysteic acid.

2. A liposome according to claim 1, wherein the chemical linkage is through a linking agent coupled to the phosphatide and to the carnitine, aminocarnitine or cysteic acid.

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L3: Entry 6 of 13 File: USPT Sep 28, 2004

DOCUMENT-IDENTIFIER: US 6797281 B1
** See image for Certificate of Correction **
TITLE: Esters of I-carnitine or alkanoyl I-carnitines

Brief Summary Text (16):
The scientific and patent literature is rich in references to the preparation and use of liposomes; there are, however, very few references describing the use of carnitine derivatives useful for gene delivery, whereas for drug delivery no documents are available dealing with known techniques for the preparation of compounds remotely resembling those according to the invention described herein.

Brief Summary Text (17):
Patent application EP 0 279 887 describes the use of a derivative of carnitine, i.e. phosphatidyl carnitine, optionally in mixtures with other phospholipids and lipids (cholesterol, phosphatidyl choline, phosphatidyl serine), for the preparation of liposomes.

Brief Summary Text (18):
In the example provided regarding the preparation of liposomes, liposomes of phosphatidyl carnitine are produced which incorporate propranolol, a drug known to be active as an antihypertensive, anti-angina and antiarrhythmia agent. The carnitine derivative is used here on account of the pronounced myocardial tropism of carnitine. This tropism makes it possible to avoid the liposomes being metabolised by the liver, rather than reaching the desired target site.

Brief Summary Text (19):
The presence of phosphatidyl carnitine also makes it possible to administer the liposomes orally, since they are resistant to intestinal lipases.

Detailed Description Text (32):
According to the present invention, the compounds of formula (II) are esters of L-carnitine, useful for the preparation of liposomes which possess potent activity in drug delivery and present characteristics of stability and selectivity in reaching the target organ comparable to those of the compounds of formula (I) described above. The same advantageous properties are applicable in case of cosmetics.

Detailed Description Text (55):
According to the present invention, the compounds of formula (III) are esters of L-carnitine, useful for the preparation of liposomes which possess potent activity in promoting drug delivery and present characteristics of stability and selectivity in reaching the target organ comparable to those of the compounds of formula (I) described above.

Detailed Description Text (191):
Preparation of Liposomes of Palmitoyl L-carnitine Chloride Undecyl Ester (ST 983) in the Form of

Current US Original Classification (1):
424/450

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L9: Entry 63 of 70 File: PGPB Oct 24, 2002

DOCUMENT-IDENTIFIER: US 20020155432 A1
TITLE: Genetically engineered herpes virus for the treatment of cardiovascular disease

Summary of Invention Paragraph:
[0007] A variety of vectors have been used to transfer genes to vascular tissue, with variable results. Each of the most popular vector systems--naked plasmid DNA (Isner et al., Hum. Gene Ther. 7:989-1011, 1996; Baumgartner et al., Circ. 97:1114-1123, 1998], liposome-encapsulated DNA, [Armeanu et al., Mol. Ther. 1:366-375, 2000] retrovirus [Geary et al., Hum. Gene Ther. 5:1211-1216, 1994], adeno-associated virus (AAV) [Lynch et al., Circ. Res. 80:497-505, 1997], and adenovirus [Kay, J. Vasc. Surg. 24:160-161, 1996; Yeh et al., FASEB J. 11:615-623, 1997], have met with some success depending on the application. Efforts at gene transfer using only naked plasmid DNA have met with limited success due to low transfection efficiency [Baumgartner et al., Circ. 97:1114-1123, 1998; Reissen et al., Hum. Gene Ther. 4:449-458, 1993; Turunen et al., Gene Ther. 6:6-11, 1999]. DNA encapsulated within liposomes is somewhat more efficient [Armeanu et al., Mol. Ther. 1:366-375, 2000; Turunen et al., Gene Ther. 6:6-11, 1999; Takeshita et al., J. Clin. Invest. 93:652-661, 1994; Lim et al., Circ. 83:2007-2011, 1991; Matsumoto et al., J. Vasc. Surg. 27:135-144, 1998; Matsumura et al., J. Surg. Res. 85:339-345, 1999] but generally lacks complete penetrance with an intact basement membrane. Retrovirus was tested in early experiments [Nabel et al., Science 244:1342-1344, 1989; Dunn et al., Circ. 99:3199-3205, 1996], as well as more recently to transfer antisense oligonucleotides [Zhu et al., Circ. 96:628-635, 1997], but suffers greatly from its low efficiency in non-dividing cells. A relatively new vector system, adeno-associated virus (AAV), has been shown to efficiently infect skeletal muscle without inciting an intense immune response [Muzyczka, Curr. Topics Microbiol. Immunol. 158:97-129, 1992], and preliminary results have demonstrated that AAV is capable of transfecting vascular EC's [Lynch et al., Circ. Res. 80:497-505, 1997; Rolling et al., Gene Ther. 4:757-761, 1997; Kotin, Hum. Gene. Ther. 5:793-801, 1994; Xiao et al., J. Virol. 70:8098-8108, 1996] smooth muscle cells (SMC's, Rolling et al., Gene Ther. 4:757-761, 1997), and cardiocytes [Svensson et al., Circ. 99:201-205, 1999]. A recent report, however, indicates that gene transfer into vascular tissue with an intact endothelium may be problematic, with only 1-14% of cells staining positive after 30 days [Eslami et al., J. Vasc. Surg. 31:1149-1159, 2000].

Summary of Invention Paragraph:
[0017] In a preferred embodiment the cardiovascular condition is hypertension in a vascular tissue. Preferably, the cardiovascular condition is selected from the group consisting of chronic heart failure, hypertensive cardiovascular disease, ischemic heart disease, arrhythmia, congenital heart disease, valvular heart disease or stenotic defect, cardiomyopathy, aneurysm, chronic venous insufficiency, peripheral arterial disease, or restenosis.

Summary of Invention Paragraph:
[0072] In preferred embodiments, the therapeutic nucleic acid will be effective in treating a vascular or cardiovascular disease or condition. A cardiovascular disease or condition which may benefit from administration of a vector of the present invention includes, but is not limited to, chronic heart failure,

hypertensive cardiovascular disease, ischemic heart disease, arrhythmia, congenital heart disease, valvular heart disease or stenotic defect, cardiomyopathy, aneurysm, chronic venous insufficiency, peripheral arterial disease or a combination thereof.

Summary of Invention Paragraph:
[0131] Suitable methods for nucleic acid delivery for transformation of an organelle, a cell, a tissue or an organism for use with the current invention are believed to include virtually any method by which a herpes virus vector can be introduced into an organelle, a cell, a tissue or an organism, as described herein or as would be known to one of ordinary skill in the art. Such methods include, but are not limited to, direct delivery of a nucleic acid such as by ex vivo transfection (Wilson et al., 1989, Nabel et al, 1989), injection (U.S. Pat. Nos. 5,994,624, 5,981,274, 5,945,100, 5,780,448, 5,736,524, 5,702,932, 5,656,610, 5,589,466 and 5,580,859, each incorporated herein by reference), including microinjection (Harlan and Weintraub, 1985; U.S. Pat. No. 5,789,215, incorporated herein by reference); by electroporation (U.S. Pat. No. 5,384,253, incorporated herein by reference; Tur-Kaspa et al., 1986; Potter et al., 1984); by calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe et al., 1990); by using DEAE-dextran followed by polyethylene glycol (Gopal, 1985); by direct sonic loading (Fechheimer et al., 1987); by liposome-mediated transfection (Nicolau and Sene, 1982; Fraley et al., 1979; Nicolau et al., 1987; Wong et al., 1980; Kaneda et al., 1989; Kato et al., 1991) and receptor-mediated transfection (Wu and Wu, 1987; Wu and Wu, 1988); by microprojectile bombardment (PCT Patent Application Publication Nos. WO 94/09699 and 95/06128; U.S. Pat. Nos. 5,610,042; 5,322,783 5,563,055, 5,550,318, 5,538,877 and 5,538,880, and each incorporated herein by reference), and any combination of such methods. Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

Summary of Invention Paragraph:
[0136] C.3. Liposome-Mediated Transfection

Summary of Invention Paragraph:
[0137] In a further embodiment of the invention, a nucleic acid may be entrapped in a lipid complex such as, for example, a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, 1991). Also contemplated is a nucleic acid complexed with Lipofectamine (Gibco BRL) or Superfect (Qiagen).

Summary of Invention Paragraph:
[0138] Liposome-mediated nucleic acid delivery and expression of foreign DNA in vitro has been very successful (Nicolau and Sene, 1982; Fraley et al., 1979; Nicolau et al., 1987). The feasibility of liposome-mediated delivery and expression of foreign DNA in cultured chick embryo, HeLa and hepatoma cells has also been demonstrated (Wong et al., 1980).

Summary of Invention Paragraph:
[0139] In certain embodiments of the invention, a liposome may be complexed with a hemagglutinating virus (HVJ). This has been shown to facilitate fusion with the cell membrane and promote cell entry of liposome-encapsulated DNA (Kaneda et al., 1989). In other embodiments, a liposome may be complexed or employed in conjunction with nuclear non-histone chromosomal proteins (HMG-1) (Kato et al., 1991). In yet further embodiments, a liposome may be complexed or employed in conjunction with both HVJ and HMG-1. In other embodiments, a delivery vehicle may comprise a ligand and a liposome. A preferred delivery vehicle comprises a liposome and a ligand

selective or, more preferably, specific for a vascular cell-specific binding partner such as a receptor.

Summary of Invention Paragraph:
[0143] In other embodiments, a nucleic acid delivery vehicle component of a cell-specific nucleic acid targeting vehicle may comprise a specific binding ligand in combination with a liposome, as described above. The nucleic acid(s) to be delivered are housed within the liposome and the specific binding ligand is functionally incorporated into the liposome membrane. The liposome will thus specifically bind to the receptor(s) of a target cell and deliver the contents to a cell. Such systems have been shown to be functional using systems in which, for example, epidermal growth factor (EGF) is used in the receptor-mediated delivery of a nucleic acid to cells that exhibit upregulation of the EGF receptor.

Summary of Invention Paragraph:
[0144] In still further embodiments, the nucleic acid delivery vehicle is a liposome itself, which will preferably comprise one or more lipids or glycoproteins that direct cell-specific binding. For example, lactosyl-ceramide, a galactose-terminal asialganglioside, have been incorporated into liposomes and observed to result in an increase in the uptake of the insulin gene by hepatocytes (Nicolau et al., 1987). It is contemplated that the tissue-specific transforming constructs of the present invention are specifically delivered into a target cell in a similar manner.

Summary of Invention Paragraph:
[0174] Non-limiting examples of miscellaneous antihyperlipoproteinemics include acifran, azacosterol, benfluorex, .beta.-benzalbutyramide, carnitine, chondroitin sulfate, clomestrone, detaxtran, dextran sulfate sodium, 5,8, 11, 14, 17-eicosapentaenoic acid, eritadenine, furazabol, meglutol, melinamide, mytatrienediol, ornithine, .gamma.-oryzanol, pantethine, pentaerythritol tetraacetate, a-phenylbutyramide, pirozadil, probucol (lorelco), .beta.-sitosterol, sultosilic acid-piperazine salt, tiadenol, triparanol and xenbucin.

Summary of Invention Paragraph:
[0277] A pharmaceutical composition comprising a herpes virus vector and/or additional agent(s) may exploit different types of carriers depending on whether it is to be administered in solid, liquid or aerosol form, and whether it need be sterile for such routes of administration as injection. The pharmaceutical compositions can be administered intravenously, intradermally, intraarterially, intra-graft, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, intramuscularly, intraperitoneally, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, orally, topically, locally, inhalation (e.g. aerosol inhalation), injection, infusion, continuous infusion, localized perfusion bathing target cells directly (e.g., in an autogenous tissue graft), via a catheter, via lavage, in cremes, in lipid compositions (e.g., liposomes), or by any other method or any combination of the foregoing as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed., Mack Printing Company, 1990).

Summary of Invention Paragraph:
[0282] In embodiments where the pharmaceutical composition is in a liquid form, a carrier can be a solvent or dispersion medium including, but not limited to, water, ethanol, polyol (e.g., glycerol, propylene glycol, liquid polyethylene glycol, etc.), lipids (e.g., triglycerides, vegetable oils, liposomes) and combinations thereof. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin; by the maintenance of the required particle size by dispersion in carriers such as, for example liquid, polyol or lipids; by the use of surfactants such as, for example, hydroxypropylcellulose; or combinations thereof.

In many cases, it will be preferable to include isotonic agents, such as sugars, sodium chloride or combinations thereof.

Detail Description Paragraph:
[0407] Ghosh and Bachhawat, "Targeting of liposomes to hepatocytes," In: Liver Diseases, Targeted Diagnosis and Therapy Using Specific Receptors and Ligands, Wu and Wu (Eds.), Marcel Dekker, New York, pp 87-104, 1991.

Detail Description Paragraph:
[0438] Isner, Walsh, Symes, Pieczek, Takeshita, Lowry, Rossow, Rosenfield, Weir, Brogi, Schainfeld, "Arterial gene therapy for therapeutic angiogenesis in patients with peripheral artery disease," Circ, 91:2687-2692, 1995.

Detail Description Paragraph:
[0450] Kato et al., "Expression of hepatitis .beta. virus surface antigen in adult rat liver. Co-introduction of DNA and nuclear protein by a simplified liposome method," J Biol Chem., 266(6):3361-3364, 1991.

Detail Description Paragraph:
[0485] Matsumoto, Komori, Yonemitsu, Morishita, Sueishi, Kaneda, Sugimachi, "Hemagglutinating virus of Japan-liposome-mediated gene transfer of endothelial cell nitric oxide synthase inhibits intimal hyperplasia of canine vein grafts under conditions of poor runoff," J Vasc Surg, 27:135-144, 1998.

Detail Description Paragraph:
[0499] Nicolau and Sene, "Liposome-mediated DNA transfer in eukaryotic cells: dependence of the transfer efficiency upon the type of liposomes used and the host cell cycle stage," Biochem. Biophys. Acta, 721:185-190, 1982.

Detail Description Paragraph:
[0500] Nicolau et al., "Liposomes as carriers for in vivo gene transfer and expression," Methods Enzymol., 149:157-176, 1987.

Detail Description Paragraph:
[0501] Nicolau, LePape, Soriano, Fargette, Juhel, "In vivo expression of rat insulin after intravenous administration of the liposome-entrapped gene for rat insulin I," Proc Natl Acad Sci, 80:1068-1072, 1983.

Detail Description Paragraph:
[0555] Takeshita, Gal, Leclerc, Pickering, Riessen, Weir, Isner, "Increased gene expression after liposome-mediated arterial gene transfer associated with intimal smooth muscle cell proliferation," J Clin Invest, 93:652-661, 1994.

Detail Description Paragraph:
[0599] Wong et al., "Appearance of .beta.-lactamase activity in animal cells upon liposome mediated gene transfer," Gene, 10:87-94, 1980.

CLAIMS:

25. The method of claim 16, wherein the cardiovascular disease or condition is selected from the group consisting of chronic heart failure, hypertensive cardiovascular disease, ischemic heart disease, arrhythmia, congenital heart disease, valvular heart disease or stenotic defect, cardiomyopathy, aneurysm, chronic venous insufficiency, peripheral arterial disease, or restenosis.

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DOCUMENT-IDENTIFIER: US 5919474 A
TITLE: Transurethral administration of vasoactive agents to treat peripheral vascular disease, related vascular diseases, and vascular impotence associated therewith

Brief Summary Text (7):
PVD has been treated medically with some success, using agents such as pentoxifylline, which acts by increasing red cell membrane deformability, thereby reducing blood viscosity (Porter et al. (1982) Am. Heart J. 104:66), although other investigators have not found such viscosity-reducing agents to be efficacious (Mashiah et al. (1978) Br. J. Surg. 65:342). Other approaches in the treatment of PVD have employed oral, parenteral or intravenous administration of vasodilators (Hansteen et al. (1974) Acta Med. Scand. [Suppl.] 556:3, Coffmann et al. (1972) Ann. Intern. Med. 76:35), L-carnitine (U.S. Pat. No. 4,968,719 to Brevetti), diuretics such as 1,3-di-n-butyl-7-(2-oxypropyl)xanthine (U.S. Pat. No. 4,784,999 to Angersbach et al.), xanthines and xanthine derivatives (U.S. Pat. Nos. 5,321,029 to Maschler et al. and 4,454,138 to Goring), selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase ("cGMP PDE") (U.S. Pat. No. 5,272,147 to Bell et al.), and various classes of chromanols, chromenes and chromans having anti-hypertensive activity (U.S. Pat. No. 4,772,603 to Evans). However, each approach has achieved limited success. Accordingly, there remains a need in the art to provide a more effective method of treating PVD, and particularly PVD-associated vascular impotence.

Detailed Description Text (21):
The active agent is, as explained above, administered in a pharmaceutical formulation suitable for transurethral drug delivery. The formulation contains one or more selected carriers or excipients, such as water, silicone, waxes, petroleum jelly, polyethylene glycol ("PEG"), propylene glycol ("PG"), liposomes, sugars such as mannitol and lactose, and/or a variety of other materials, with polyethylene glycol and derivatives thereof particularly preferred.

Detailed Description Text (60):
Individuals are assessed and pre-screened to assemble an experimental group of subjects suffering from intermittent claudication. Each individual is affected by peripheral arterial insufficiency at the second stage of Fontaine's classification (i.e., claudication on effort without pain at rest and/or trophic in an affected leg) for at least a year prior to enrollment in the study. Ankle/brachial systolic blood pressure ratio is obtained by Doppler ultrasound. Blood perfusion is measured by impedance plethysmography using the method of Nyober et al. (1974) A. Heart J. 87:704, and calculated from an average of five consecutive waves. Walking distance before the occurrence of claudication is measured on a treadmill and expressed as absolute walking distance (AWD) which indicates the maximum distance in meters walked by the individual at an average speed 2.5 mph on a grade of 7 degrees.

Other Reference Publication (3):
Hansteen et al. (1974), "Vasodilator Drugs in the Treatment of Peripheral Arterial Insufficiency," Acta Med. Scand. [Suppl.] 556:3.

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